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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 08/716,209 | 10/09/1996 | LAURENT PRADIER | ST94014-US | 5539 |

29693 7590 11/23/2001

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| EXAMINER |
|---|
| GUCKER, STEPHEN |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | 31 |

DATE MAILED: 11/23/2001

Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 08/716,209 | Pradier et al. |
| **Examiner** | **Group Art Unit** |
| Stephen Gucker | 1647 |

*—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

**Status**

☑ Responsive to communication(s) filed on _____.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

☑ Claim(s) 27-28, 31-35, 37-38, 40-54 is/are pending in the application.

Of the above claim(s) 42-47 & 51-54 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☑ Claim(s) 27-28, 31-35, 37-38, 40-41, & 48-50 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☑ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119 (a)-(d)**

☑ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

All ☑ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: FR94/03191.

**Attachment(s)**

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☑ Notice of Reference(s) Cited, PTO-892

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Interview Summary, PTO-413

☐ Notice of Informal Patent Application, PTO-152

☐ Other _____

**Office Action Summary**

***Response to Amendment***

**1.** A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/14/01 has been entered.

**2.** The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

**3.** Any objections or rejections made in a previous Office Action that are not herein reinstated have been withdrawn.

**4.** The disclosure is objected to because of the following informalities: The first sentence of the specification claims the benefit under 35 USC 120 and 365(c) of co-pending US Application Serial No. 08/403,868. However, the first sentence of the specification fails to identify if the instant Application is a continuation, divisional, or a continuation-in-part of 08/403,868.

Appropriate correction is required to claim the benefit.

**5.** The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321© may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this

application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**6.** Claims 27-28, 31-35, 37-38, 40-41, and 48-50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 57-62, 66-70, 72-74, 79-80, and 82 of copending Application No. 08/403,868. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending Application No. 08/403,868 are co-extensive with and encompass the instant claims of the instant Application. The claims of the instant Application are drawn to the genus of an adenovirus encoding brain-derived neurotrophic factor while the co-pending claims of Application No. 08/403,868 are drawn to the genus of an adenovirus encoding neurotrophic factors. The genus of brain-derived neurotrophic factors comprises the majority of the species of the genus comprised of neurotrophic factors as most neurotrophic factors can be found in the brain where they are derived.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

**7.** The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371© of this title before the invention thereof by the applicant for patent.

(f) he did not himself invent the subject matter sought to be patented.

**8.** Claims 27-28, 31-35, 37-38, 40-41, and 48-50 are rejected under 35 U.S.C. § 102(f) because the applicants did not invent the claimed subject matter. The claimed products encompassing a replication defective recombinant adenovirus comprising a cDNA encoding brain-derived neurotrophioc factor (BDNF) are disclosed in foreign priority document EP92-402644.6, filed September 25, 1992. It is noted that this same foreign priority document is the priority document in WO 94/08026, which is the published international application also known as PCT/EP93/02519 which was recited in the first sentence of the specification and the inventorship of WO 94/08026 is Axel Kahn, Jacques Mallet, Michel Perricaudet, Marc Peschanski, Jean-Jacques Robert, and Le Gal La Salle which differs from the instant inventive entity. The claimed invention is set forth in the foreign priority document and WO 94/08026, but the inventorship of WO 94/08026 is different from the instant Application even though both the instant Application and WO 94/08026 claim benefit of the same foreign priority document. Because of this ambiguity concerning the inventorship of the foreign priority document, it is incumbent on applicants to provide a satisfactory showing which would lead to a reasonable conclusion that applicants alone are the inventors of the claimed invention. To resolve the ambiguity, applicants may file declarations by the non-applicant co-authors of the references disclaiming the invention or a declaration by applicants setting forth the facts which provide an explanation as to why the non-applicants Axel Kahn, Jacques Mallet, Marc Peschanski, Jean-Jacques Robert, and Le Gal La Salle are not inventors. Applicant is reminded of the requirement

for identity of inventorship between a U.S. application and a 35 U.S.C. 119 priority application. See MPEP § 201.13 and 2137.01.

**9.** All of the instant claims recite or depend from claims which recite the limitation of an adenovirus E1 gene which is non-functional. However, neither foreign priority document EP92-402644.6, filed September 25, 1992, or WO 94/08026, which is the published international application also known as PCT/EP93/02519, filed September 17, 1993, disclose an E1 gene which is non-functional. The aforementioned priority documents describe an adenovirus where the E1 gene is merely lacking or deleted, which is distinguished from non-functional in the instant Application (see pages 9-10 of the instant specification). Therefore, in addition to the 102(f) rejection set forth above, none of the instant claims receive the benefit of any effective filing priority before 3/2/95, the filing date of PCT/FR95/00250. Applicant cannot rely upon the foreign priority paper FR94/03191, filed 3/18/94, because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

**10.** The Examiner is making a request for information under 37 CFR 1.105. The G. Le Gal La Salle reference of record (*Science, Vol. 259*, 12 February 1993, pages 988-990) has a co-inventor of the instant Application, M. Perricaudet, as a co-author. A replication defective adenovirus for gene transfer into mammalian neurons is described in the *Science* publication. However, the *Science* publication omits key details as to how this adenovirus was made replication defective. Based on Applicants' other published work, it is the Examiner's position that the adenovirus described in the *Science* publication has a deleted or non-functional E1 gene, at least one of the

E2, E4, or L1-L5 genes was nonfunctional, comprised an ITR and a sequence permitting encapsulation, and the adenovirus was type Ad 2 or Ad 5. The Examiner requests confirmation of this by Applicants or an explanation as to how the adenovirus described in the *Science* publication co-authored by M. Perricaudet was made replication defective if the E1 gene was not involved and how it does not meet the claim limitations of the instant invention. See MPEP § 704.11(a), Example (I).

**11.** Claims 27-28, 31-35, 37-38, 40-41, and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barde in view of Le Gal La Salle for reasons of record and the following. Barde discloses an adenovirus encoding human prepro/BDNF cDNA and transfected mammalian cells (column 18, line 32 to column 20, line 53, and column 38, line 7 to column 40, line 18). Barde did not teach specialized viral promoters for the nervous system or non-functional adenovirus E1 gene. Le Gal La Salle discloses replication deficient adenovirus vectors for gene transfer into neurons and glia that use RSV-LTR promoters and GFAP (page 988). Le Gal La Salle does not teach adenovirus comprising prepro/BDNF encoding cDNA. Le Gal La Salle also had Michel Perricaudet as a co-author, who is also a co-inventor of the instant application. It is the Examiner's position that the replication deficient adenovirus of Le Gal La Salle had a non-functional E1 gene and meets all other claim limitations, absent evidence to the contrary. It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the encoding nucleotide sequences for BDNF and adenovirus vector of Barde and the replication deficient adenovirus of Le Gal La Salle in order to treat diseases of the

nervous system amenable to BDNF treatment or to produce BDNF protein as suggested by Barde (column 25, line 44 to column 29, line 42) and because replication deficient adenovirus cannot multiply once introduced to the brain, thereby avoiding a potentially uncontrollable viral infection of the brain, as mentioned by Le Gal La Salle ("nonreplicative infection" as an asset, page 988), as well as avoiding lytic destruction of neurons from replicating virus. The motivation to use the RSV-LTR or GFAP promoters is to increase the yield of the encoding nucleotides to produce BDNF protein.

*Applicant's arguments filed 8/14/01 have been fully considered but they are not persuasive. Applicant has not perfected the foreign filing date sought of 9/25/92, so the Le Gal La Salle reference is still held as prior art (2/12/93).*

**12.** Claims 27-28, 31-35, 37-38, 40-41, and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barde in view of Wilson et al. (US 5,585,362). Barde discloses an adenovirus encoding human prepro/BDNF cDNA and transfected mammalian cells (column 18, line 32 to column 20, line 53, and column 38, line 7 to column 40, line 18). Barde did not teach specialized viral promoters for the nervous system or non-functional adenovirus E1 gene. Wilson teaches replication-defective adenovirus (abstract), RSV-LTR promoter, Ad 5 human adenovirus (column 11, lines 54-65), and human cells from lung (column 8, lines 66-67). Wilson does not teach adenovirus comprising prepro/BDNF encoding cDNA. The filing date of Wilson is 6/7/93 and that date is now considered the effective filing date of Wilson in regards as a reference for the instant Application. It would have been obvious to one of ordinary skill in the

art at the time the invention was made to use the encoding nucleotide sequences for BDNF and adenovirus vector of Barde and combine that with the replication deficient adenovirus of Wilson because Wilson discloses many advantages for the adenovirus vector for gene therapy, including its approval for clinical trials (column 2, lines 25-26), growth to extremely high titers for production purposes, usefulness in nondividing cells (column 2, lines 58-60) such as neurons (brain cells), and other reasons (column 1, lines 54-62). In addition, replication deficient adenovirus cannot multiply once introduced to the brain, thereby avoiding a potentially uncontrollable viral infection of the brain, as well as avoiding lytic destruction of neurons from replicating virus. The motivation to use the RSV-LTR promoter is to increase the yield of the encoding nucleotides to produce BDNF protein.

*Applicant's arguments filed 8/14/01 have been fully considered but they are not persuasive. Applicant has not perfected the foreign filing date sought of 9/25/92, so Wilson is still held as prior art (6/7/93) under 102(e).*

**13.** Claims 27-28, 31-34, 37, 41, and 48-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barde in view of Levrero et al. ("Levrero"). Barde discloses an adenovirus encoding human prepro/BDNF cDNA and transfected mammalian cells (column 18, line 32 to column 20, line 53, and column 38, line 7 to column 40, line 18). Barde did not teach specialized viral promoters for the nervous system or non-functional adenovirus E1 gene. Levrero teaches replication-defective adenovirus with defective E1 genes (abstract), MLP promoter (abstract), Ad 5 human adenovirus (page 197) and human cells including hepatocytes

or liver-derived cells (pages 197-200). Levrero does not teach adenovirus comprising prepro/BDNF encoding cDNA. It would have been obvious to one of ordinary skill in the art at the time the invention was made to make and use the BDNF encoding adenovirus of Barde as a replication defective adenovirus as taught by Levrero in order to treat diseases of the nervous system amenable to BDNF treatment or to produce BDNF protein as suggested by Barde (column 25, line 44 to column 29, line 42) and because replication deficient adenovirus cannot multiply once introduced to the brain, thereby avoiding a potentially uncontrollable viral infection of the brain and avoiding lytic destruction of neurons from replicating virus. In addition, Levrero teaches that defective adenovirus usually produced higher amounts of protein product than nondefective virus (page 198), providing further motivation as to the choice of defective virus over nondefective. The motivation to use the MLP promoter is to increase the yield of the encoding nucleotides to produce BDNF protein.

**14.** Claims 27-28, 31-33, 37, 41, and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barde in view of Quantin et al. ("Quantin"). Barde discloses an adenovirus encoding human prepro/BDNF cDNA and transfected mammalian cells (column 18, line 32 to column 20, line 53, and column 38, line 7 to column 40, line 18). Barde did not teach specialized viral promoters for the nervous system or non-functional adenovirus E1 gene. Quantin teaches replication-defective adenovirus with defective E1 genes, Ad 5 human adenovirus (pages 2581-2582) and human cells (pages 2581-2582). Quantin does not teach adenovirus comprising prepro/BDNF encoding cDNA. It would have been obvious to one of

ordinary skill in the art at the time the invention was made to make and use the BDNF encoding adenovirus of Barde as a replication defective adenovirus as taught by Quantin in order to treat diseases of the nervous system amenable to BDNF treatment or to produce BDNF protein as suggested by Barde (column 25, line 44 to column 29, line 42) and because replication deficient adenovirus cannot multiply once introduced to the brain, thereby avoiding a potentially uncontrollable viral infection of the brain and avoiding lytic destruction of neurons from replicating virus.

**15.** Claims 27-28, 31-35, 37, 41, and 48-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barde in view of Stratford-Perricaudet et al. ("Stratford-Perricaudet"). Barde discloses an adenovirus encoding human prepro/BDNF cDNA and transfected mammalian cells (column 18, line 32 to column 20, line 53, and column 38, line 7 to column 40, line 18). Barde did not teach specialized viral promoters for the nervous system or non-functional adenovirus E1 gene. Stratford-Perricaudet teaches replication-defective adenovirus with defective E1 genes (page 627), the RSV-LTR promoter (page 626), Ad 5 human adenovirus (page 626) and human cells (pages 626). Stratford-Perricaudet does not teach adenovirus comprising prepro/BDNF encoding cDNA. It would have been obvious to one of ordinary skill in the art at the time the invention was made to make and use the BDNF encoding adenovirus of Barde as a replication defective adenovirus as taught by Stratford-Perricaudet in order to treat diseases of the nervous system amenable to BDNF treatment or to produce BDNF protein as suggested by Barde (column 25, line 44 to column 29, line 42) and because replication deficient adenovirus cannot multiply

once introduced to the brain, thereby avoiding a potentially uncontrollable viral infection of the brain and avoiding lytic destruction of neurons from replicating virus. The motivation to use the RSV-LTR promoter is to increase the yield of the encoding nucleotides to produce BDNF protein.

**16.** No claim is allowed.

**17.** Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Gucker whose telephone number is (703) 308-6571. The examiner can normally be reached on Monday to Friday from 0830 to 1700. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz, can be reached on (703) 308-4623. The fax phone number for this Group is currently (703) 308-4242, but Applicant should confirm this by phoning the Examiner before faxing.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SG

Stephen Gucker

November 16, 2001

Gary L. Kunz

GARY L. KUNZ
SUPERVISORY PATENT EXAMINER
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